INSELGRUPPE

Symposium CHUV, 28.9.2023

What registry data contributed to intracerebral haemorrhage research

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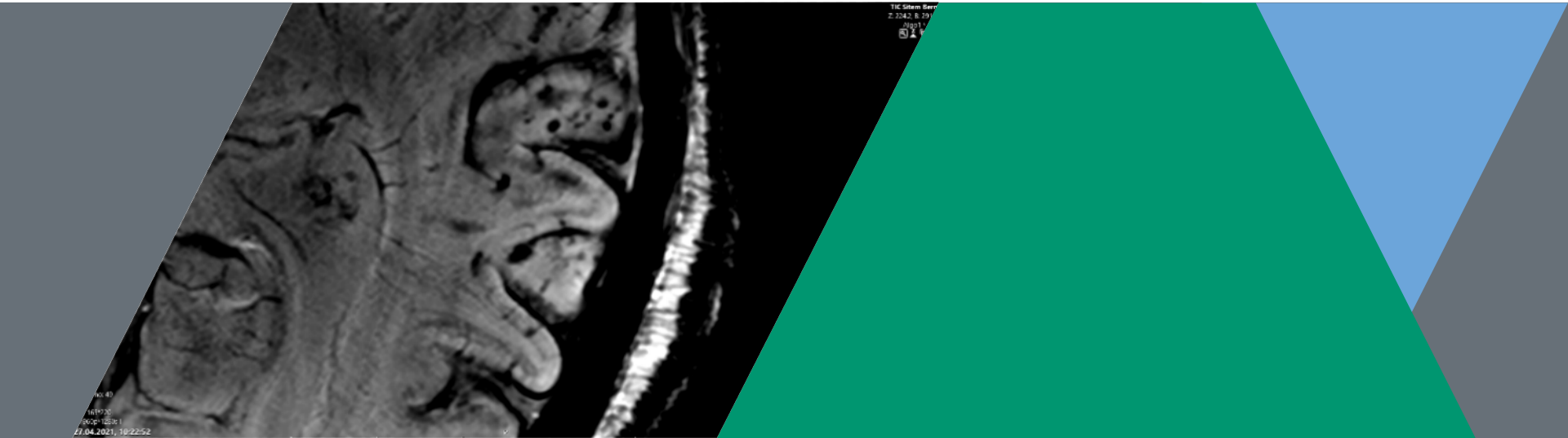


Disclosures

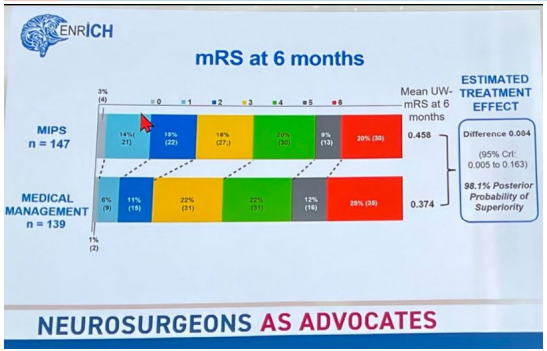
Research funding

- Swiss National Science Foundation, Swiss Heart Foundation, Bangerter-Rhyner Foundation, AstraZeneca (Externally sponsored research program)

Speaker/Advisory board (used for research funding)

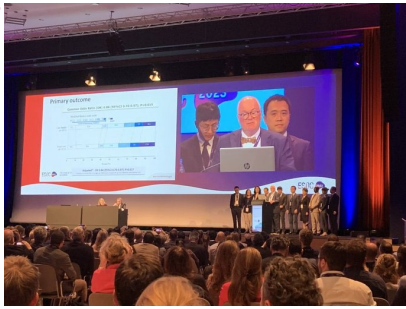
- AstraZeneca, Pfizer, VarmX, Bioxodes, ECMREG

2023 – THE year for intracerebral haemorrhage treatment



The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial

Lu Ma, Xin Hu*, Lili Song*, Xiaoying Chen*, Menglu Ouyang, Laurent Billot, Qiang Li, Alejandra Malavera, Xi Li, Paula Muñoz-Venturelli, Asita de Silva, Nguyen Huy Thang, Kolawole W Wahab, Jeyaraj D Pandian, Mohammad Wasay, Octavio M Pontes-Neto, Carlos Abanto, Antonio Arauz, Haiping Shi, Guanghai Tang, Sheng Zhu, Xiaochun She, Leibo Liu, Yuki Sakamoto, Shoujiang You, Qiao Han, Bernard Crutzen, Emily Cheung, Yunke Li, Xia Wang, Chen Chen, Feifeng Liu, Yang Zhao, Hao Li, Yi Liu, Yan Jiang, Lei Chen, Bo Wu, Ming Liu, Jianguo Xu, Chao You, Craig S Anderson, for the INTERACT3 Investigators†*



Andexxa Phase IV trial stopped early after achieving pre-specified criteria on haemostatic efficacy versus usual care

ANNEXa I

PUBLISHED
5 June 2023

In 2023, 3(!) positive RCTs for treatment of ICH have been published, presented or announced

History of (mainly unsuccesful) RCTs in ICH management

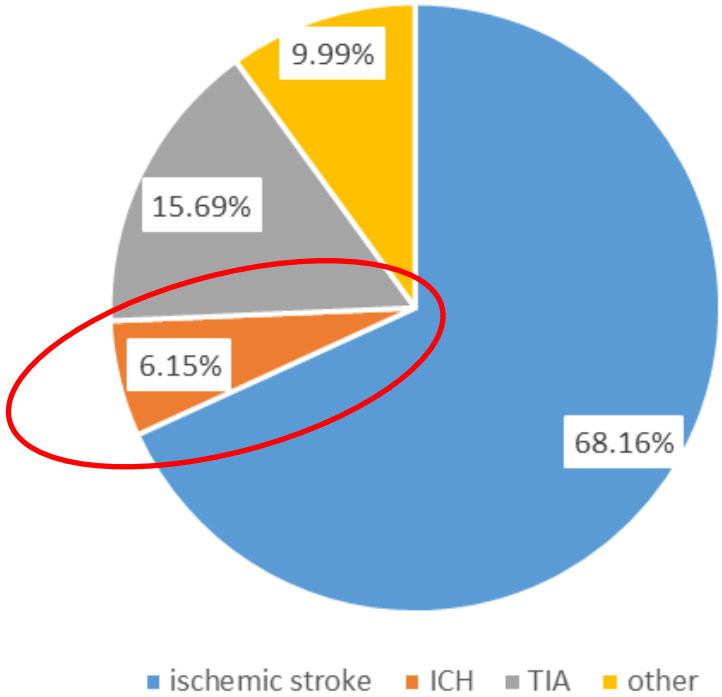
	NNT
• 1993: stroke unit	18
• 2005: surgery (STICH)	-
• 2008: rFactor VIIa (FAST)	-
• 2013: surgery (STICH II)	-
• 2013: intensive BP lowering (Interact2)	28
• 2016: very intensive BP lowering (ATACH-II)	-
• 2016: thrombocytes (on antiplatelets. PATCH)	harm
• 2018: tranexamic acid (TICH-2)	-
• 2019: deferoxamine (i-DEF; phase 2)	-
• 2019: minimally invasive surgery with rtPA (MISTIE III)	-

History of (mainly unsuccesful) RCTs in ICH management

	NNT
• **2023: care bundle* (Interact3)** **BP lowering, strict glucose controle, antipyrexia, rapid reversal anticogulation**	**35**
• **2023: min. invasive, trans-sulcal, parafasc. surgery (ENRICH)** **Lobar ICH only**	**11?**

- 2024: hemicraniectomy (SWITCH)
- 2025: rFactorVIIa <2hrs (FASTEST)
- 2025: minimally invasive endoscopy guided surgery (EVACUATE)
- 2026: minimally invasive endoscopy guided surgery (DIST; MIND)
- 2029: tranexamic acid (TICH-3)

The Swiss Stroke Registry (29.12.2022 – 83137 patients)



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JoS
JOURNAL OF STROKE

Check for updates

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Original Article

Etiology, 3-Month Functional Outcome and Recurrent Events in Non-Traumatic Intracerebral Hemorrhage

Martina B. Goeldlin,[a,b] Achim Mueller,[c] Bernhard M. Siepen,[a,b] Madlaine Mueller,[a] Davide Strambo,[d] Patrik Michel,[d] Michael Schaerer,[e] Carlo W. Cereda,[f] Giovanni Bianco,[f] Florian Lindheimer,[g] Christian Berger,[g] Friedrich Medlin,[h] Roland Backhaus,[i] Nils Peters,[i] Susanne Renaud,[j] Loraine Fisch,[k] Julien Niederhaeuser,[k] Emmanuel Carrera,[l] Elisabeth Dirren,[l] Christophe Bonvin,[m] Rolf Sturzenegger,[n] Timo Kahles,[o] Krassen Nedeltchev,[o] Georg Kaegi,[p] Jochen Vehoff,[p] Biljana Rodic,[q] Manuel Bolognese,[r] Ludwig Schelosky,[s] Stephan Salmen,[a,t] Marie-Luise Mono,[u] Alexandros A. Polymeris,[v] Stefan T. Engelter,[v,w] Philippe Lyrer,[v] Susanne Wegener,[c] Andreas R. Luft,[c,x] Werner Z'Graggen,[a,y] David Bervini,[y] Bastian Volbers,[a,z] Tomas Dobrocky,[aa] Johannes Kaesmacher,[b,aa,bb] Pasquale Mordasini,[aa] Thomas R. Meinel,[a,b] Marcel Arnold,[a] Javier Fandino,[cc] Leo H. Bonati,[v] Urs Fischer,[v] David J. Seiffge,[a] on Behalf of the SSR Investigators

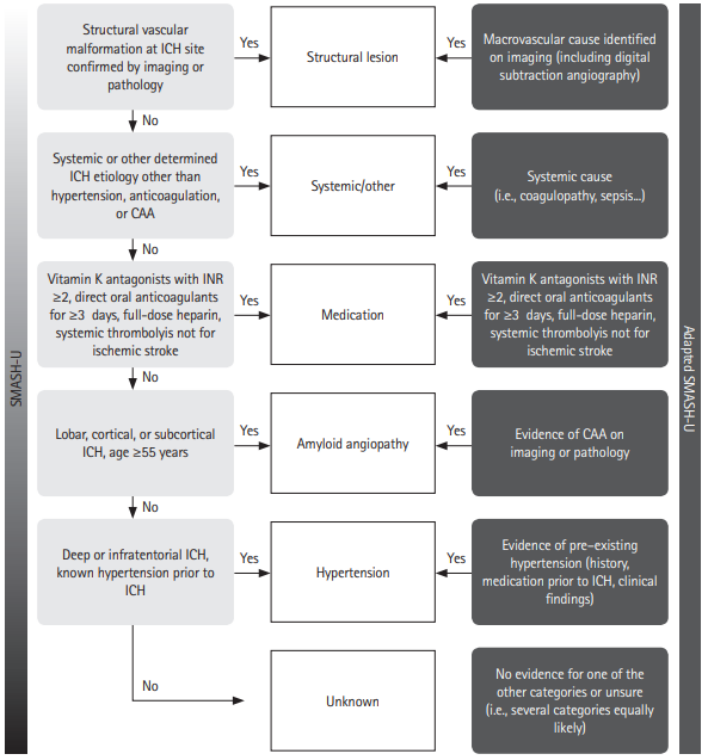


Figure 1. Mechanistic classification of intracerebral hemorrhage (ICH) etiology: comparison of the original and adapted SMASH-U (structural lesion > systemic disease > medication > amyloid angiopathy > hypertension > unknown) classifications. CAA, cerebral amyloid angiopathy; INR, international normalized ratio.

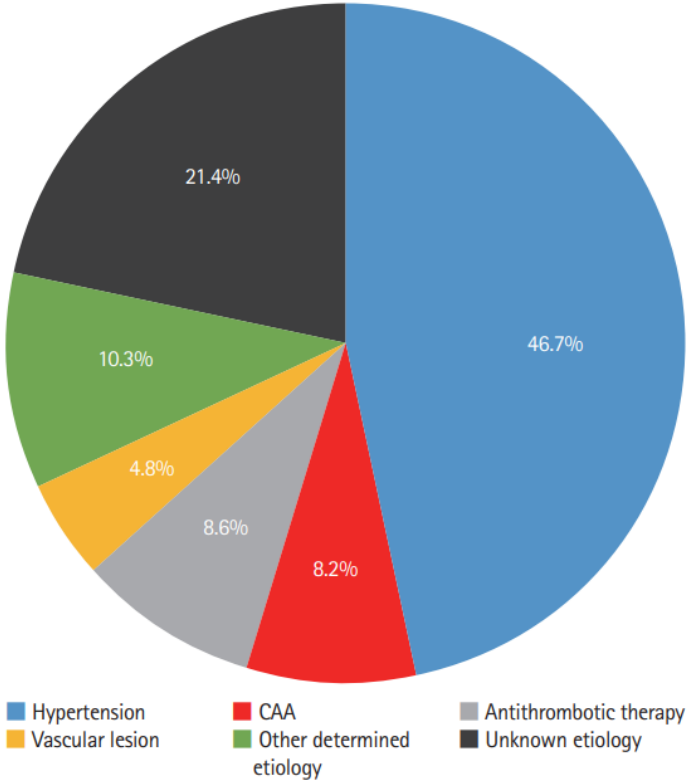
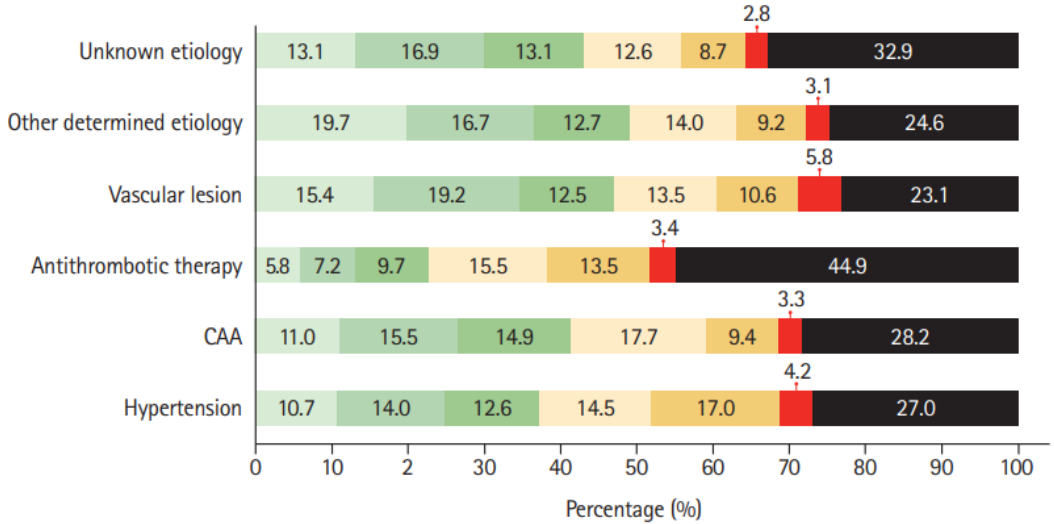


Figure 2. Frequency of intracerebral hemorrhage etiologies. CAA, cerebral amyloid angiopathy.

Table 1. Baseline characteristics of the cohort and distribution among subgroups according to intracerebral hemorrhage etiology

Characteristic	Total (n=2,650)	Hypertension (n=1,238, 46.7%)	Antithrombotic (n=227, 8.6%)	CAA (n=217, 8.2%)	Macrovascular (n=128, 4.8%)	Other determined etiology (n=274, 10.3%)	Unknown (n=566, 21.4%)	*P*
Demographics								
Age (yr)	71.9±14.1	72.6±13.0	78.5±9.8	77.1±8.2	59.3±17.5	66.1±17.6	70.8±14.3	<0.001
Female sex	1,227 (46.5)	541 (43.9)	95 (42.0)	122 (56.2)	52 (40.6)	133 (48.5)	284 (50.5)	0.002
Risk factors								
Hypertension	2,053 (79.9)	1,152 (95.0)	189 (84.8)	147 (71.0)	57 (46.7)	164 (62.4)	344 (63.4)	<0.001
Diabetes	384 (15.0)	198 (16.3)	43 (19.3)	27 (13.1)	14 (11.4)	40 (15.4)	62 (11.4)	0.033
Hyperlipidemia	1,096 (43.1)	535 (44.5)	105 (48.2)	91 (44.6)	41 (33.3)	102 (39.7)	222 (41.3)	0.071
Smoking	306 (12.0)	142 (11.7)	26 (11.7)	15 (7.3)	17 (13.9)	40 (15.5)	66 (12.3)	0.154
Atrial fibrillation	467 (18.2)	174 (14.4)	137 (61.4)	22 (10.6)	7 (5.7)	43 (16.7)	84 (15.5)	<0.001
Concomitant medication								
Antiplatelets	729 (28.6)	368 (31.0)	46 (20.4)	71 (33.8)	28 (22.2)	66 (25.6)	150 (27.9)	0.004
Anticoagulation	568 (22.3)	193 (16.3)	212 (93.4)	24 (11.4)	8 (6.3)	51 (19.8)	80 (14.9)	<0.001
DOAC	241 (42.4)	99 (51.3)	74 (34.9)	12 (50.0)	3 (37.5)	18 (35.3)	35 (43.8)	
VKA	296 (52.1)	87 (45.1)	128 (60.3)	10 (41.6)	5 (62.5)	27 (52.9)	39 (48.8)	
Others*	31 (5.4)	7 (3.6)	10 (4.7)	2 (8.3)	0 (0)	6 (11.8)	6 (7.5)	
Medical history								
History of ischemic stroke	290 (11.3)	139 (11.5)	38 (16.7)	30 (14.5)	13 (10.5)	25 (9.6)	45 (8.3)	0.009
History of transient ischemic attack	116 (4.5)	50 (4.1)	13 (5.8)	14 (6.8)	1 (0.8)	8 (3.1)	30 (5.5)	0.068
History of intracerebral hemorrhage	280 (10.9)	97 (8.0)	28 (12.6)	65 (31.4)	8 (6.5)	23 (8.8)	59 (10.9)	<0.001
Clinical presentation on admission								
NIHSS on admission	8 (3–15)	9 (4–16)	10 (3–17)	5 (2–12)	7 (1–15)	4 (1–11)	6 (2–15)	<0.001
GCS on admission	15 (12–15)	14 (12–15)	14 (12–15)	15 (14–15)	15 (10–15)	15 (14–15)	15 (12–15)	0.003
Systolic blood pressure on admission (mm Hg)	166.3±31.6	176.3±31.0	161.3±29.9	157.0±26.5	155.0±33.6	154.8±28.7	158.7±29.8	<0.001
Diastolic blood pressure on admission (mm Hg)	90.8±26.3	96.1±33.1	89.0±18.2	84.2±14.9	86.7±20.5	85.2±17.2	86.2±16.9	<0.001
Management								
Treatment at stroke center	2,052 (77.4)	1,000 (80.8)	174 (76.7)	167 (77.0)	92 (71.9)	182 (66.4)	437 (77.2)	<0.001
MRI performed	969 (42.5)	347 (32.3)	55 (29.7)	105 (57.1)	65 (57.5)	137 (59.6)	260 (52.6)	<0.001
Onset-to admission time (hr)	3.8 (1.4–13.3)	2.8 (1.2–10.0)	4.0 (1.3–13.3)	7.5 (2.1–23.6)	4.7 (1.1–16.2)	5.6 (1.6–24.0)	5.2 (1.6–14.8)	<0.001
Discharge destination								
Home	460 (21.8)	187 (18.4)	18 (11.3)	40 (22.7)	25 (24.5)	74 (32.7)	116 (26.9)	<0.001
Nursing home or palliative care	143 (6.8)	65 (6.4)	19 (11.9)	21 (11.9)	5 (4.9)	7 (3.1)	26 (6.0)	
Other acute care hospital	380 (18.0)	175 (17.2)	29 (18.2)	22 (12.5)	23 (22.5)	46 (20.4)	85 (19.7)	
Rehabilitation hospital	1,129 (53.5)	590 (58.0)	93 (58.5)	93 (52.8)	49 (48.0)	99 (43.8)	205 (47.5)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
CAA, cerebral amyloid angiopathy; DOAC, direct oral anticoagulants; VKA, vitamin K antagonist; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow coma scale; MRI, magnetic resonance imaging.
*Parenteral anticoagulation.



>1/3 good outcome

~30% mortality

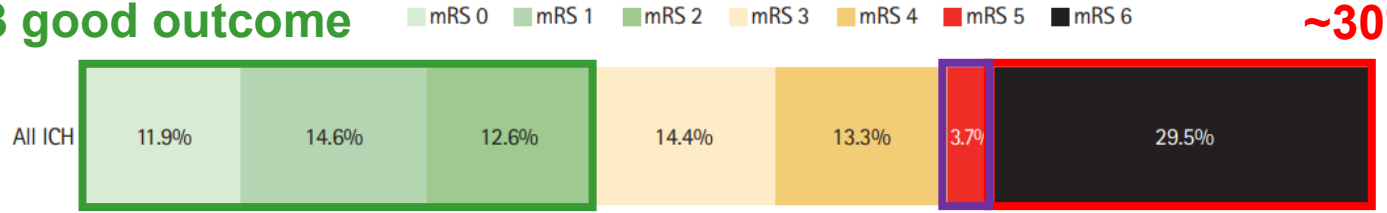
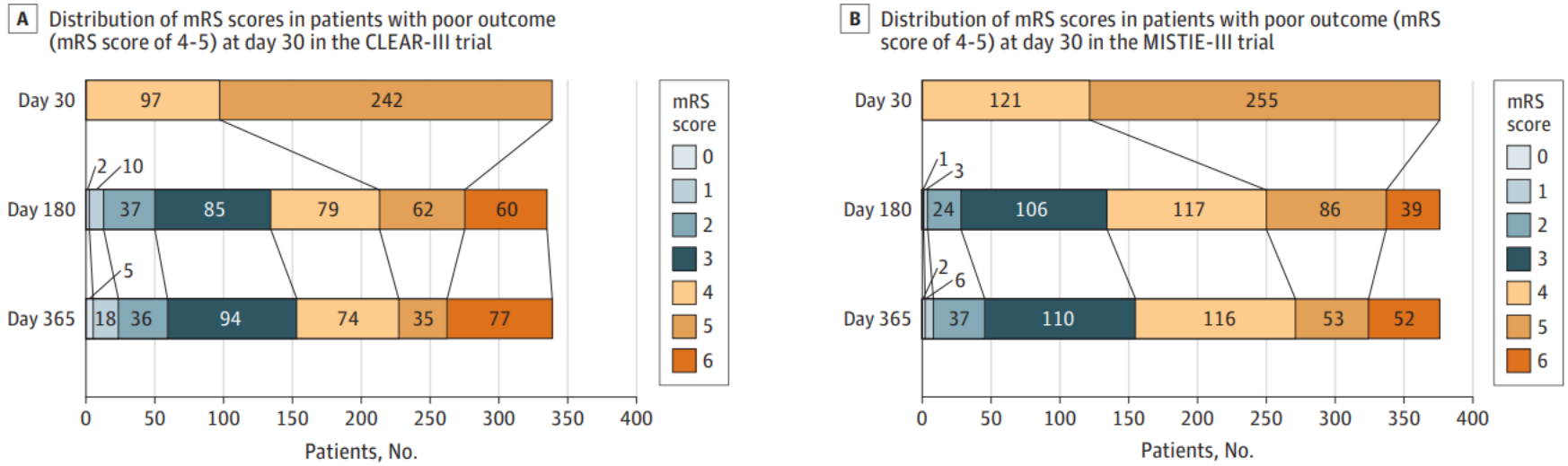


Figure 4. Functional outcomes at 3 months according to intracerebral hemorrhage (ICH) etiology. CAA, cerebral amyloid angiopathy; mRS, modified Rankin Scale.

<4% «bad» outcome

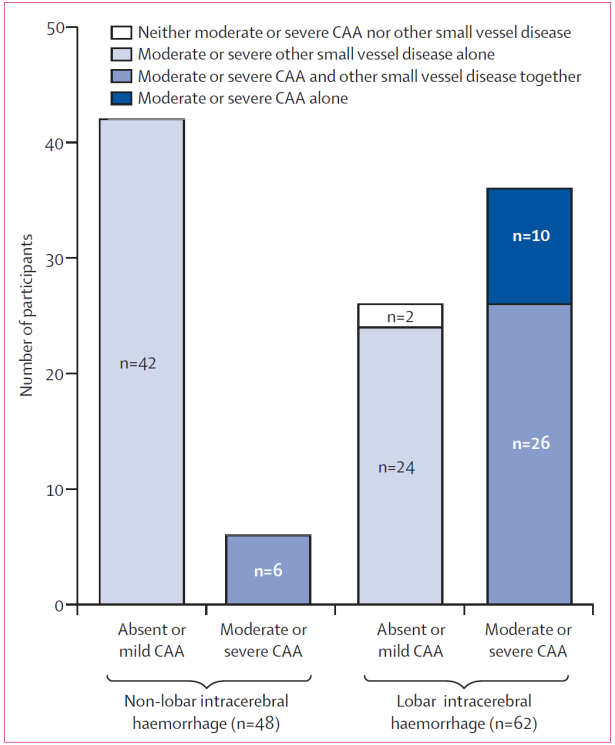
3 – months outcome: too short after ICH?

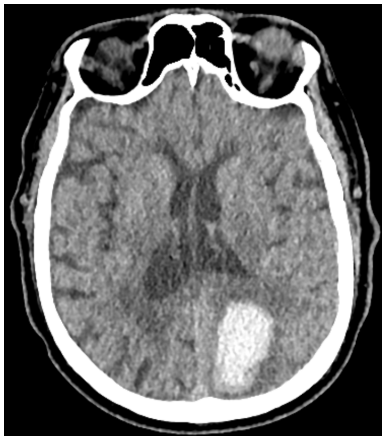
Figure 2. Ordinal Distribution of Modified Rankin Scale Score (mRS) at Serial Time Points in Patients With Poor Outcomes at Day 30 in the CLEAR-III and MISTIE-III cohorts

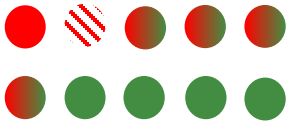


Shah et al JAMA Neurology 2022

Frequency of CAA-related ICH – autopsy data







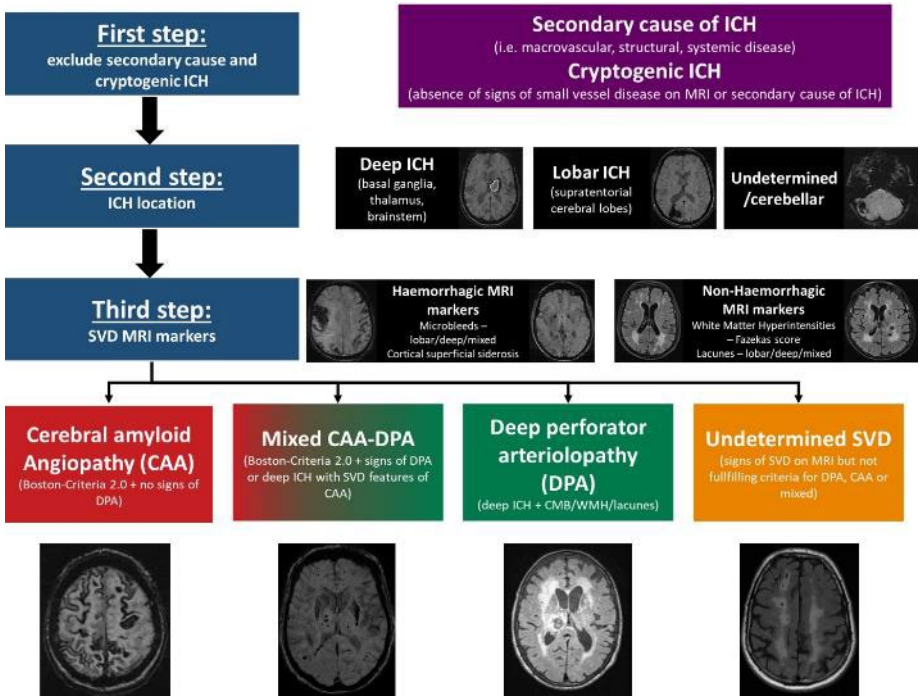
CAA

Mixed CAA/DPA

DPA

Rodrigues et al Lancet Neurology 2018

MRI-based classification: CADMUS



17% undetermined

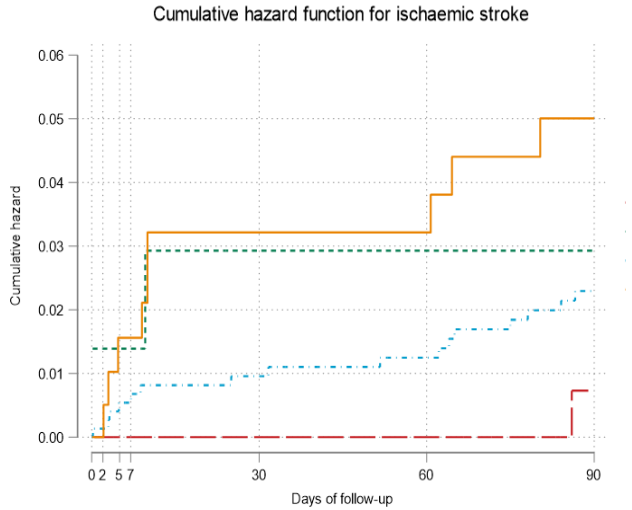
6% DPA

63% mixed CAA-DPA

13% CAA

Goeldlin et al accepted

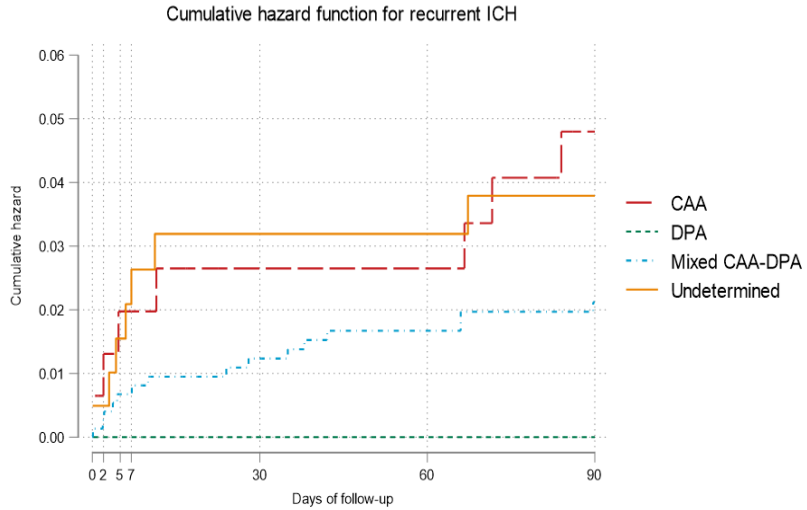
MRI-based classification: CADMUS



Number at risk

CAA	154	148	145	143	142	142	141	140	139	136
DPA	72	64	64	63	63	63	63	63	63	63
Mixed CAA-DPA	751	720	706	697	686	682	676	669	667	662
Undetermined	203	181	176	174	170	169	169	166	166	165

a



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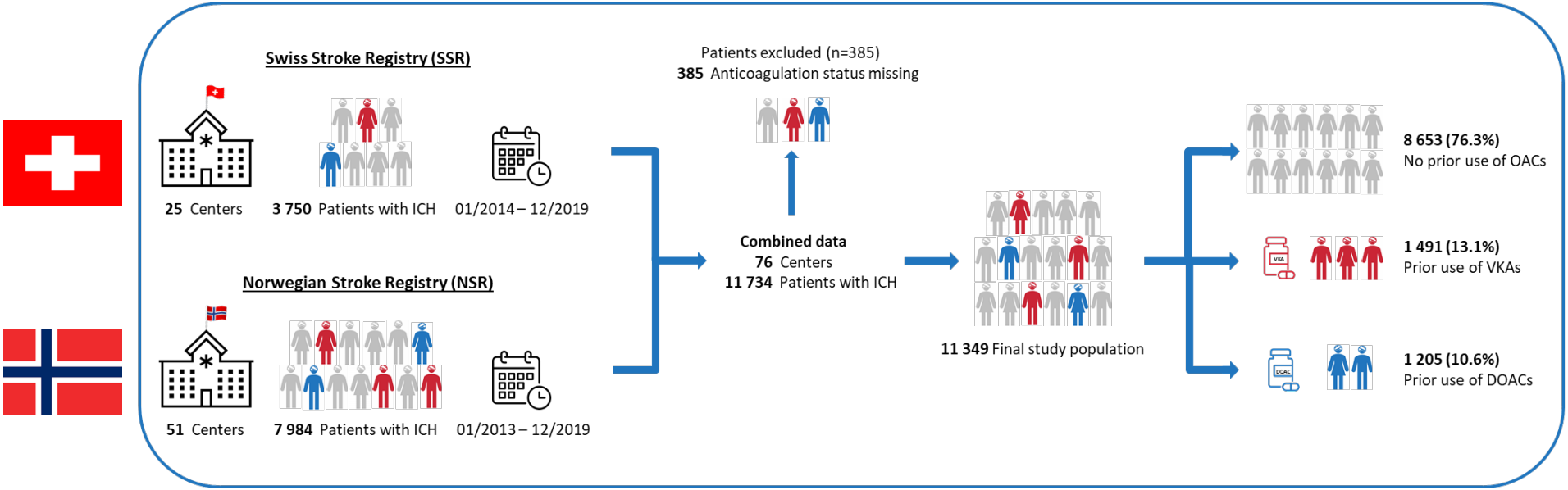
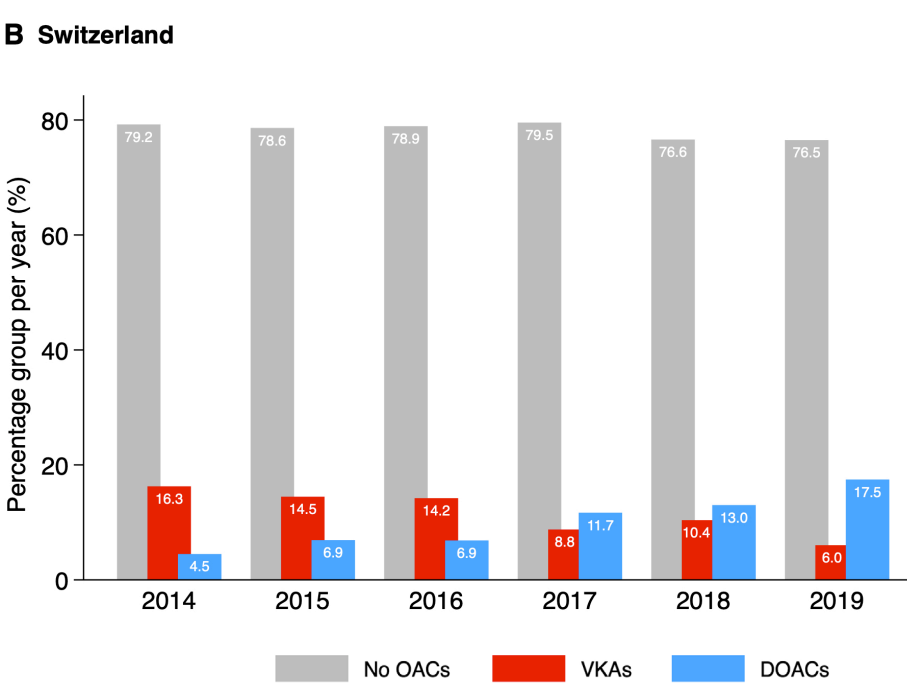
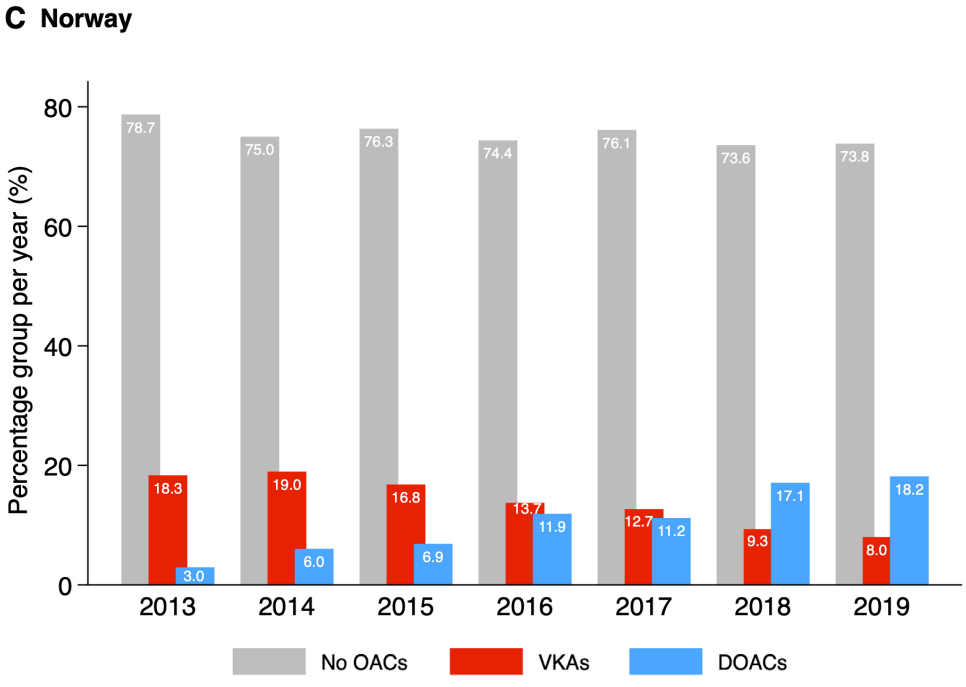
b

Intracerebral haemorrhage in patients taking different types of oral anticoagulants – a pooled individual patient data analysis from two national stroke registries



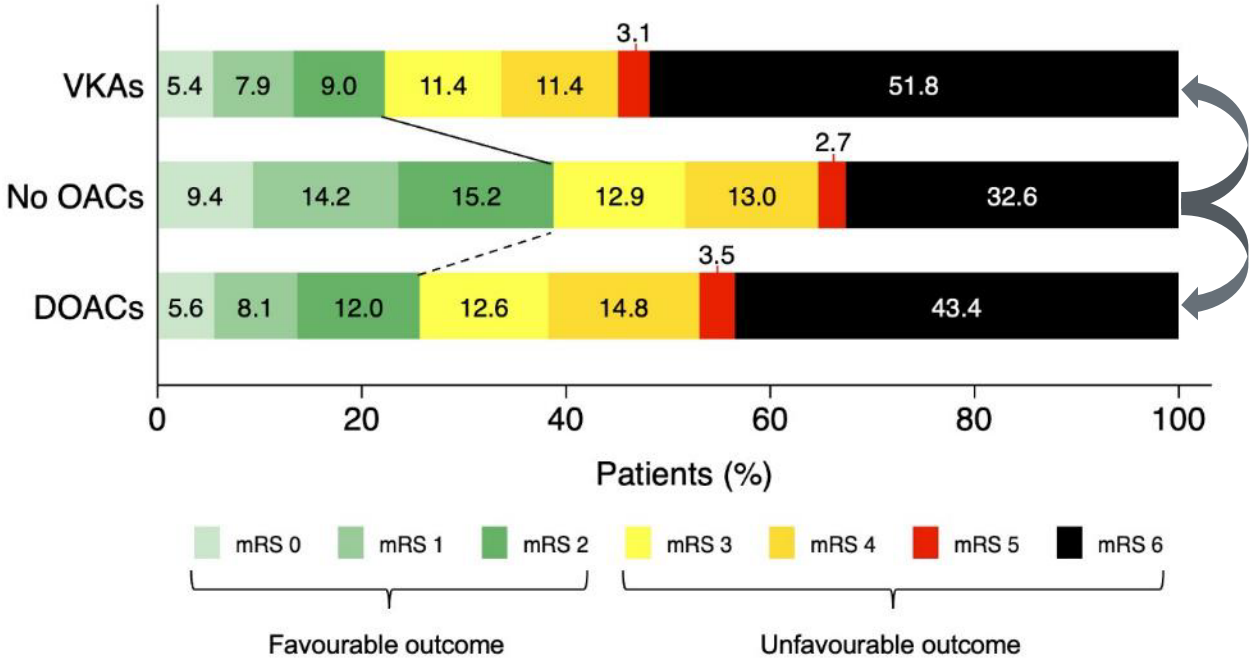
Frequency of different types of anticoagulants in patients with ICH





Siepen et al under review

3-months outcomes in patients with OAC-associated ICH



aOR 0.75, 95%CI 0.59-0.97

aOR 0.92, 95%CI 0.70-1.21

Siepen et al under review

Research Article

EUROPEAN STROKE JOURNAL

European Stroke Journal
1–12

DOI: 10.1177/23969873231193237
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Small vessel disease burden and risk of recurrent cerebrovascular events in patients with lacunar stroke and intracerebral haemorrhage attributable to deep perforator arteriolopathy

Martina B Goeldlin[1,2*], Jan Vynckier[1,3*], Madlaine Mueller[1,2], Boudewijn Drop[1], Basel Maamari[1], Noah Vonlanthen[1], Bernhard M Siepen[1,2], Arsany Hakim[4], Johannes Kaesmacher[4], Christopher Marvin Jesse[5], Mandy D Mueller[5], Thomas R Meinel[1], Morin Beyeler[1,2], Leander Clénin[1], Jan Gralla[4], Werner Z'Graggen[1,5], David Bervini[5], Marcel Arnold[1], Urs Fischer[1,6] and David J Seiffge[1]

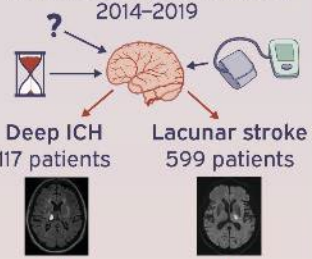
EUROPEAN STROKE JOURNAL

Small vessel disease burden and risk of recurrent cerebrovascular events in patients with lacunar stroke and intracerebral hemorrhage attributable to deep perforator arteriolopathy

Do disease burden on MRI, functional outcome and recurrence rate differ between intracerebral hemorrhage (ICH) versus lacunar stroke, if associated with deep perforator arteriolopathy?

Methods

Prospective Stroke Registry 2014–2019



Small vessel disease burden
Functional outcome
Recurrent events

Results

ICH compared to lacunar stroke:

↑ SVD burden score: aOR_{shift} 3.19

↑ mRS: aOR_{shift} 2.16

⟷ Similar 3-month recurrence rates

Conclusion

More severe deep perforator arteriolopathy manifesting as ICH compared to lacunar stroke

Poorer functional outcome in deep ICH compared to lacunar stroke

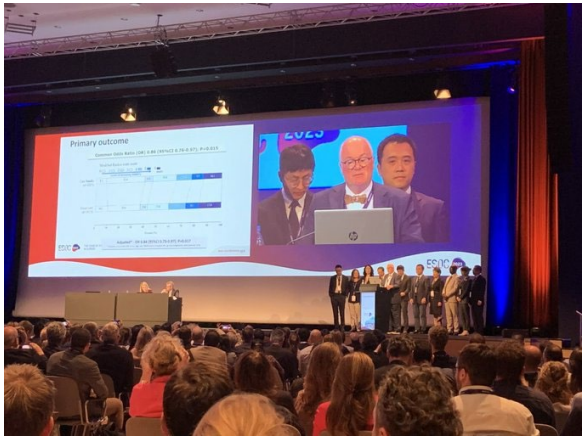
No difference in recurrence rates

Goeldlin M. B., et al. European Stroke Journal, 2023 david.seiffge@insel.ch doi.org/10.1177_23969873231193237

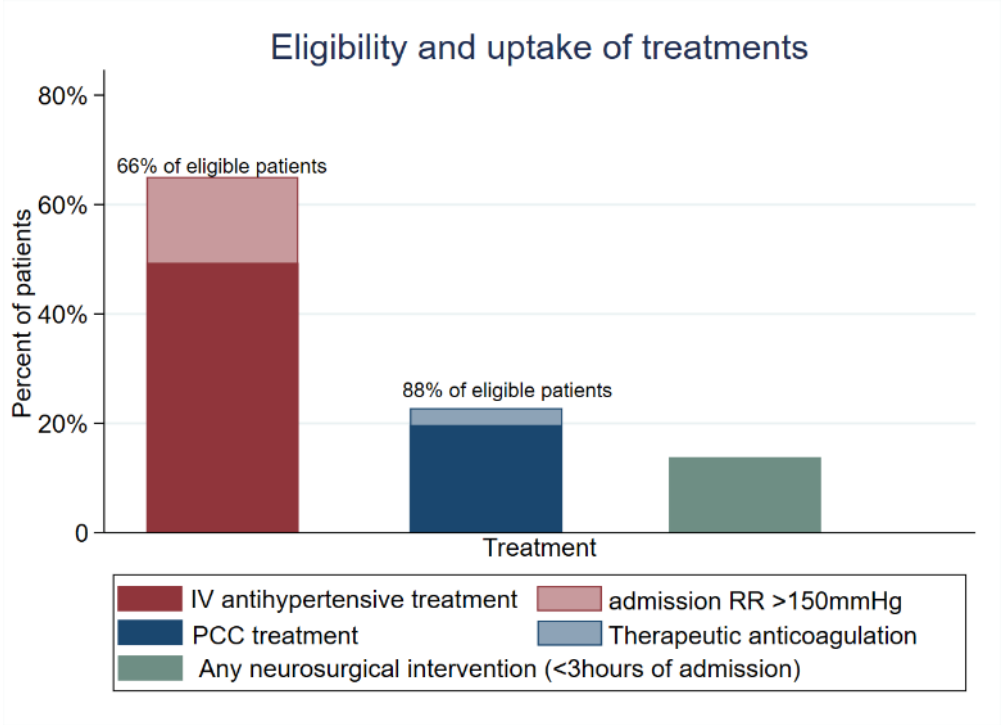
Care bundle care for ICH

The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial

Lu Ma, Xin Hu*, Lili Song*, Xiaoying Chen*, Menglu Ouyang, Laurent Billot, Qiang Li, Alejandra Malavera, Xi Li, Paula Muñoz-Venturelli, Asita de Silva, Nguyen Huy Thang, Kolawole W Wahab, Jeyaraj D Pandian, Mohammad Wasay, Octavio M Pontes-Neto, Carlos Abanto, Antonio Arauz, Haiping Shi, Guanghai Tang, Sheng Zhu, Xiaochun She, Leibo Liu, Yuki Sakamoto, Shoujiang You, Qiao Han, Bernard Crutzen, Emily Cheung, Yunke Li, Xia Wang, Chen Chen, Feifeng Liu, Yang Zhao, Hao Li, Yi Liu, Yan Jiang, Lei Chen, Bo Wu, Ming Liu, Jianguo Xu, Chao You, Craig S Anderson, for the INTERACT3 Investigators†*



Care bundle delivery at Inselspital Bern



Care bundle metrics at Inselspital Bern

	Admission	Imaging	IV antihypertensive	PCC	ED discharge
					
all patients	27 min (IQR 18-52)	38 min (IQR 18-72)	59 min (IQR 37-111)	139 min (IQR 85-220)	
stroke code	23 min (IQR 18-35)	61 min (IQR 34-84)	63 min (IQR 45-85)	157 min (IQR 111-220)	
transfer		18 min (IQR 9-38)	37 min (IQR 17-85)	103 min (IQR 59-173)	
other	33 min (IQR 18-86)	50 min (IQR 26-136)	70 min (IQR 41-240)	203 min (IQR 98-317)	

Summary

- After years of failure, in 2023 3 RCTs in ICH have been positive
- Observational studies contributed to our current knowledge about clinical characteristics, prognosis and management of ICH patients
- Swiss Stroke Registry is a useful tool to investigate ICH in Switzerland
- Swiss Stroke Registry data collection for ICH needs to be revised reflecting recent developments and specific aspects of ICH
  - Delivery and metrics of acute treatment (DNT for BP control and anticoagulation reversal!)
  - Aetiology
  - Long-term outcomes (>3 months)

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